Remarks

Claims 1, 3, 5, and 8-11 are now pending in this application. Claims 2 and 12-15 were previously cancelled. Claims 3 and 5 are currently withdrawn from consideration. Claim 4, 6, and 7 are cancelled herein. The claims currently under consideration are claims 1 and 8-11.

Applicants note with appreciation the withdrawal of various grounds of objection and rejection as set forth in paragraphs 4-6 of the Office Action.

Specification

The Action states at paragraph 7 that the term "Polybrene" is a trademark that should be capitalized wherever it appears in the specification and accompanied by the generic terminology.

A search of the TESS and TARR databases on the USPTO website indicates that the registration for this mark, Reg. No. 574098, was not renewed and expired on February 7, 1994. As the mark is no longer registered, it is respectfully submitted that no amendment to the specification is required. Further, "polybrene" is hexadimethrine bromide, as shown in *The Merck Index*, thirteenth ed., p. 836, entry 4702 (Exhibit A hereto). Accordingly, it is respectfully submitted that one skilled in the art will have a full understanding of what is meant by the term "polybrene" as used in the specification, and no amendment to the specification is required.

Rejections Under 35 U.S.C. § 112, First Paragraph

Claims 1, 4, and 6-11 stand rejected for lack of written description in the specification, in that the recited claim limitations "R2" and "R3" allegedly encompass a genus of molecules not adequately described in the specification. The Examiner states that claims 6 and 8 also invoke a genus of molecules which lack adequate written description.

Without acquiescing in these grounds of rejection, but solely to further prosecution of this application, claim 1 is amended to incorporate therein the limitations of claims 4, 6, and 7, namely, that R2 comprises a chromogenic substrate which is a peptide substrate for thrombin, and R3 comprises heparin. Claims 4, 6, and 7 are accordingly cancelled. Claim 8 is amended herein to delete "an accelerator of the interaction between AT and thrombin" and insert therefor "heparin." It is respectfully submitted that the language of claims 1 and 8 as amended finds ample support in the specification, and it is respectfully requested that this ground of rejection be withdrawn.

Rejections Under 35 U.S.C. § 112, Second Paragraph

Claims 1, 4, and 6-11 are rejected as being indefinite with respect to the claim language "free thrombin," the examiner noting that in step (a) "the thrombin essentially does not interact with AT but interacts with the one or more pharmaceutical compounds that inhibit thrombin…." The Examiner states that the thrombin that reacts with the "one or more pharmaceutical compounds" must be "bound" to those compounds, and is therefore not "free" thrombin. Without acquiescing in this ground of rejection, claim 1 is amended at step (b) and step (d) to replace the words "free thrombin" with the words "thrombin not interacting with AT." It is respectfully submitted that support for this amendment is found at paragraphs [0008]-[0010] of the originally filed specification of the present application. No change in the scope of the claim is intended by this amendment, and no new matter is added. It is respectfully submitted that this amendment is sufficient to overcome this ground of rejection.

In paragraph 12 of the Office Action, the Examiner states that "the difference between the first and second determinations" in step (e) lacks antecedent basis. Accordingly, the claim is amended so that the step of determining the difference between the first and second determinations is affirmatively recited in step (e), and new step (f) affirmatively recites the step of determining the AT content in the sample from said difference determined in step (e). No change in the scope of the claim is intended by this amendment, and no new matter is added.

In paragraph 13, the Examiner notes that the preamble states that the "one or more pharmaceutical compounds" may be present, but that step (a) requires that said compounds react with the thrombin. Accordingly, claim 1 has been amended to recite that the thrombin reacts with said one or more compounds "if present." This amendment is made to make the body of the claim consistent with the preamble. No new matter is added by this amendment, and no change in the scope of the claim is intended.

In paragraph 14 of the Office action, it is noted that claim 9 contains the term "polybrene." As noted above in the context of the specification, the federal registration for "Polybrene" expired 15 years ago. Nevertheless, to expedite prosecution of the application, claim 9 is amended herein to delete the term "polybrene" and substitute therefore the term "hexadimethrine bromide," which is understood by those skilled in the art to be the meaninig of this term, as shown at Exhibit A. No change in the scope of the claim is intended, and no new matter is added.

In paragraph 15 of the Office Action, it is noted that claim 11 recites "the determination of thrombin," but claim 1 recites first and second determinations of thrombin, such that it is not clear which determination is being referred to in claim 11. Accordingly, claim 11 is amended to recite "said first and/or second" determination of thrombin, to clairfy that either or both determinations of thrombin are being referred to. No change in the scope of the claim is intended by this amendment, and no new matter has been added.

As all grounds of rejection under 35 USC 112 second paragraph have been met, it is respectfully requested that this ground of rejection be withdrawn.

Rejections Under 35 U.S.C. § 103

The rejection of claims 1-2, 4, 6-7, and 11 as obvious over Plattner et al. or Philo et al. in view of Winant et al., Furatu, Morris et al, and Akhavan-Tafti et al. is respectfully traversed.

One aspect of the invention lies in the surprising discovery that it is possible to conduct two reliable determinations of free thrombin successively in *one and the same sample*, and by comparing the determinations to obtain an accurate determination of AT in the sample, despite the presence of a drug in the sample which otherwise would interfere and thereby render the determination inaccurate. Also, one skilled in the art would not have expected that it would have been possible to obtain an accurate determination of AT by comparing the two thrombin measurements when the second thrombin measurement is made after the addition of the regent R3.

To the contrary, the skilled person upon reading Plattner et al. would have expected that a reliable comparison between the first and second determinations of free fractions of AT binding partner would not have been possible, due to the addition of the R3 reagent between the first and second determinations.

Specifically, in the present invention, only a *single determination of AT* is made, based on *two measurements of free thrombin in the same sample* but under different conditions. Plattner and Philo do not teach or suggest that free thrombin should be measured twice under different conditions to determine the amount of AT in *the same* sample. Nor do Plattner or Philo suggest that it is possible to determine the amount of AT in a sample when an interfering factor such as a drug is also present. In Plattner and Philo, all the color determinations are made under the same conditions.

Contrary to the Examiner (Office action page 10, last line – page 11, line 1), Plattner does not teach adding a third reagent R3 to change the conditions under which thrombin is measured;

thrombin is only measured as a function of the amount of the chromophore produced, after the addition of heparin, from which the amount of AT can be derived.

As to Winant, the fact that hirudin was known in the art as an antithrombolytic that could be used in treatment of anti-thrombin-III deficiency and other conditions does not mean that its use in an assay procedure is obvious.

As the Examiner correctly notes, Plattner et al. differs from the claimed invention in that it fails to specifically teach conducting two measurements of the same substance at different times and under different conditions in a single reaction mixture. With regard to the other cited references, applicant points out the claims as now amended are limited to detection of AT using thrombin, and none of the secondary references relates to AT or thrombin. The Furatu reference teaches more than one measurement on the same sample, but of different analytes. Furatu in the paragraph spanning pages 3-4, teaches the analysis of a "first analysis item," then adding a reagent to measure a "second analysis item," the calculation of the concentration of the "second analysis item" being corrected to account for the amount of reagent added. This does not teach comparative analyses of any *single* analyte, and certainly not of an AT binding partner under different reaction conditions to determine AT. In other words, Furatu teaches separate measurements to measure different substances, not separate measurements of the same substance under different conditions.

Similarly, the Morris reference teaches performing a test on a sample to determine the presence of ANA, and then performing other tests on the same sample to confirm the presence of a disease. Morris does not teach taking the difference between any two tests of a *single analyte* under different conditions to obtain a quantitative determination of a substance with which the analyte reacts. The Akhvan-Tafti reference also teaches taking the measurements of *two different analytes* at a single time, not using the difference between two measurements at different times and under different conditions on the same sample to determine a single analyte.

In other words, none of the cited art teaches or suggests the essence of the present invention, namely, the measurement of an analyte, in this case thrombin, under two different reaction conditions, namely without and with the presence of a reaction accelerator, on a single sample in a single reaction vessel to provide a quantitative determination of another substance in the reaction mixture, in this case AT.

Accordingly, claim 1 as currently amended is not obvious over the cited art of record

The rejection of claims 8 and 9 as obvious over Plattner et al. in view of Furatu, Morris et al., and Akhavan-Tafti and further in light of Exner is respectfully traversed. Exner is cited as teaching that polybrene is a heparin antagonist. Specifically, Exner describes the addition of Polybrene to human plasma samples in order to inhibit heparin when determining the activity of protein-C. Therefore, Exner only describes the determination of activity in those samples in which heparin is inhibited by polybrene. Exner does not describe any instances in which heparin as an active component and polybrene are both present at the same time.

The Examiner states that it would have been obvious to use polybrene in the step of measuring the progressive anti-thrombin activity as taught by Plattner. But in Plattner the step of measuring the progressive anti-thrombin activity is specifically conducted in the presence of heparin to accelerate the thrombin AT interaction; i.e., Plattner et al. specifically teach the addition of heparin to the reaction mixture, it would not be obvious to add an antagonist for a component that is specifically added. Accordingly, claims 8 and 9 of the present application are not obvious over the cited art.

In view of the foregoing, a Notice of Allowance is respectfully requested.

MCDONNELL BOEHNEN HULBERT & BERGHOFF LLP

Date: December 9, 2009

/Sandra B. Weiss/
Sandra B. Weiss
Reg. No.: 30,814

McDonnell Boehnen Hulbert & Berghoff LLP
300 South Wacker Drive
Chicago, Illinois 60606-6709
Tel: 312 913 0001
Fax: 312 913 0003